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TITLE: The Root Cause of Post Traumatic and Development Stress Disorders

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13. SUPPLEMENTARY NOTES

14. ABSTRACT

Our overarching scientific hypothesis holds that serotonergic influences on brain development driven by genetics and early experience induce a variation of normal brain anatomy that makes the brain highly susceptible to the effects of severe stress. We are studying this question using both clinical and basic approaches. New findings from our lab funded by VA support the existence of an anatomical phenotype conferring susceptibility to depression, and the current work seeks to extend these findings to PTSD. After TATRC review in January of 2011, a revised research plan was developed to include a pre/post-deployment study at Fort Hood and anatomical studies of PTSD in collaboration with NIMH, Yale and USUHS. Based on input from contracting relating to the maturation date of funds, the budget and revised proposal was resubmitted in December and the funds were released for use in June, 2012. Post-mortem brain tissue from 9 brains have been sent to NIMH for a gene expression/transcriptome study to investigate gene expression. This tissue has been combined with 6 PTSD brains from the NIMH Clinical Brain Disorder Branch whose clinical diagnosis are being verified as consistent with our diagnostic methods. Golgi methods for analysis of prefrontal anatomy have been developed at Yale and pilot studies are being completed to finalize methods. A second study of a subset of the PTSD brains indicates substantial DNA hypermethylation in the medial orbitofrontal cortex. Eight new Fort Hood staff are being trained to employ the SCID and Columbia suicide interviews and will be certified starting this month.

15. SUBJECT TERMS

None.

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INTRODUCTION:

Our overarching scientific hypothesis holds that serotonergic influences on brain development driven by genetics and early experience induce a variation of normal brain anatomy that makes the brain highly susceptible to the effects of severe stress. The new goal of Project 1 is to describe the progression of post-deployment stress disorders (PTSD, major depression, suicidality) in active duty troops using predeployment/postdeployment structured clinical interviews, and to investigate developmental and environmental factors that influence predisposition to PTSD and depression. A subset of participants will be selected to have predeployment/postdeployment MRI and psychophysiological analysis. Using DNA gathered from clinical trials, we will investigate genetic factors influencing resiliency and susceptibility to stress disorders using a panel of 20 genes that we have tested and validated. Project 2 will investigate post-mortem anatomy in subjects with major depression and/or PTSD. Both molecular and histological techniques will be employed to study the brains already collected. An overarching goal of the Program is integration of data across the projects to compare and contrast the potential for different assessment paradigms (MRI anatomy, fMRI, evoked potentials, startle, genetic profiling) to screen for resiliency and predisposition to post-traumatic and developmental stress disorder stress disorders.

BODY:

KEY RESEARCH ACCOMPLISHMENTS:

Administrative:

Approval to move forward with the redesigned Project 1 was received from TATRC and MOMRP in February, 2012 and the redesigned budget was released in June, 2012. The IRB for Project 1 has completed initial review at BAMC and is under initial review by HRPO. Approval for the post-mortem human work was received from ORP in September, 2012.

Project Specific:

Project 1:

Task 1: Sample 2000 active duty/guard troops predeployment

a. Diagnostic interview (SCID)
b. Depression symptoms
c. Stress battery (DRRI, development history, suicidality)
d. Blood for DNA/RNA
e. Medical testing (CBC/TSH/CMP)

Task 2: Resample/test post-deployment

Progress 09/21/12

Initial IRB review is completed at BAMC and the proposal has been submitted to HRPO for initial review. Seven SCID trainers haves completed training are in the process of undergoing certification by the training team. Phlebotomy training is complete and most of the trainees are now certified. Columbia Suicide Interview training is 75% complete.

Project 2 Neurobiology

Task 1: Pre-deployment/post-deployment MRI testing *300 scanning sessions*

Progress 09/21/12

IRB approval for MRI work is pending at BAMC and HRPO.

Task 2. Continue collection of PTSD, MDD and control brains

Progress 09/21/12

2 additional PTSD and 2 controls have been collected in 2011-12. In addition, 3 MDD brains were collected. Two of these brains have completed post-mortem diagnosis and contributed samples for the PTSD gene expression study.

Task 3. Compare gene expression in the frontal cortex of PTSD and controls.

Progress 09/21/12

Samples from the brains have been sent to NIMH Clinical Brain Disorders Branch to study frontal cortical gene expression in PTSD vs controls. Frontal cortical tissue (area 9/25) from 9 PTSD brains from our collection and 6 PTSD brains from NIMH are undergoing RNAseq analysis. In a subset of these brains, we have documented hypermethylation at 355 methylation sites in the medial orbitofrontal cortex in PTSD brains, compared to 25 sites in controls. We are in the process of analyzing and extending this data to include microRNA and biomarkers and will prepare an abstract for Biological Psychiatry in the spring.

Task 4. Compare anatomical markers in frontal cortex/hippocampus of PTSD, MDD and controls, with 5HTTLPR and other genetic variants as cofactors.

Progress 09/21/12

Both golgi and synaptic marker methods are under development since funding started on this project in July, 2012. Processing to provide slides for other anatomical markers is also being performed currently

REPORTABLE OUTCOMES: None
CONCLUSION: No scientific conclusions have been made at this point in time.
APPENDICES: None.